**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | |
|---|---|---|
| *In re*: Application of: Lewin *et al.* | § | Confirmation Number: 7183 |
| Appl. No. 09/847,601 | § | Examiner: Chong, Kimberly |
| Filed: May 1, 2001 | § | Group Art Unit: 1635 |
| For: Adeno-Associated Virus-Delivered Ribozyme Compositions and Methods for the Treatment of Retinal Diseases | § | Attorney Docket No.: **36689.140** (formerly 4300.014100) |

**RESPONSE TO "NOTICE OF NON-RESPONSIVE AMENDMENT" DATED JANUARY 23, 2006**

Mail Stop Amendment
Commissioner For Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This paper is submitted in response to the Notice of Non-Responsive Amendment dated January 23, 2006, for which the first date for response was February 23, 2006. A request for a three-month extension of time to respond is included herewith along with the required fee. This extension brings the due date up to and including May 23, 2006, which is within the statutory period for reply. Should such request or fee be deficient or absent, consider this paragraph such a request and authorization to withdraw the appropriate fee under 37 C. F. R. §§ 1.16 to 1.21 from Deposit Account No. 08-1394.

The Examiner is requested to enter the amendment and consider the remarks herein.

## 1. CLAIM AMENDMENTS

***This listing of claims will replace all prior versions, and listings, of claims in the application:***

1. (Original) A ribozyme that specifically cleaves an mRNA encoding a polypeptide that causes or contributes to the disease, disorder, or dysfunction of a cell or a tissue of a mammalian eye.

2. (Previously Presented) The ribozyme of claim 1, wherein said ribozyme specifically cleaves an mRNA encoding a polypeptide selected from the group consisting of rod opsin, RP1, RDS/Peripherin, iNOS, $A_{2B}$ receptor, IGF-1 receptor, alpha 1, alpha 3, and alpha V.)

3. (Original) The ribozyme of claim 2, wherein said ribozyme (a) comprises the sequence of any one of SEQ ID NO:2, or SEQ ID NO:90 to SEQ ID NO:105, or (b) specifically cleaves an mRNA comprising a sequence selected from any one of SEQ ID NO:1, or SEQ ID NO:3 to SEQ ID NO:89.

4. (Previously Presented) The ribozyme of claim 3, wherein said ribozyme comprises a sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID

NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, and SEQ ID NO:105.

5. (Previously Presented) The ribozyme of claim 2, wherein said ribozyme specifically cleaves an mRNA encoding a polypeptide selected from the group consisting of a mutant rod opsin polypeptide, a mutant RP1 polypeptide, a mutant RDS/Peripherin polypeptide, a mutant iNOS polypeptide, a mutant $A_{2B}$ receptor polypeptide, a mutant IGF-1 receptor polypeptide, a mutant alpha 1 polypeptide, a mutant alpha 3 polypeptide, and a mutant alpha V polypeptide.

6. (Withdrawn) The ribozyme of claim 5, wherein said ribozyme specifically cleaves an mRNA encoding a mutant rod opsin polypeptide.

7. (Withdrawn) The ribozyme of claim 6, wherein said ribozyme specifically cleaves an mRNA encoding a mutant rod opsin polypeptide that comprises a mutation selected from the group consisting of P23H, P23L, Q28H, F45L, L46R, G51A, G51G, G51R, G51V, P53R, T58R, Q64stop, 68-71, V87D, G90D, G106W, C110Y, G114D, R135G, R135L, R135P, P171L, P171S, Y178C, P180A, C187Y, G188R, D190G, D190Y, M207R, H211R, H211P, F220C, C264X, P267L, F220C, C222R, A292E, Q344stop, and P347S.

8. (Currently Amended) The ribozyme of claim 1~~7~~, wherein said ribozyme specifically cleaves an mRNA that comprises a nucleotide sequence selected from the group consisting of SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID

NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, and SEQ ID NO:91.

9. (Original) The ribozyme of claim 5, wherein said ribozyme specifically cleaves an mRNA encoding a mutant RP1 polypeptide, or an $A_{2B}$ reccptor polypeptide.

10. (Withdrawn) The ribozyme of claim 9, wherein said ribozyme specifically cleaves an mRNA comprising the sequence of SEQ ID NO:64 or SEQ ID NO:1.

11. (Withdrawn) The ribozyme of claim 5, wherein said ribozyme specifically cleaves an mRNA encoding a mutant RDS/Peripherin polypeptide.

12. (Withdrawn) The ribozyme of claim 11, wherein said ribozyme specifically cleaves an mRNA encoding a mutant RDS/Peripherin polypeptide that comprises a mutation

selected from the group consisting of C118, R172Q, R172W, P210R, C214S, P216L, and P219.

13. (Withdrawn) The ribozyme of claim 12, wherein said ribozyme specifically cleaves an mRNA that comprises a sequence selected from the group consisting of SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, and SEQ ID NO:77.

14. (Original) The ribozyme of claim 1, wherein said molecule is a hammerhead ribozyme.

15. (Original) The ribozyme of claim 1, wherein said molecule is a hairpin ribozyme.

16. (Original) A vector comprising a polynucleotide encoding the ribozyme of claim 1, said polynucleotide operably linked to at least a first promoter element that directs expression of said polynucleotide in a mammalian cell.

17. (Original) The vector of claim 16, wherein said vector is a viral vector.

18. (Original) The vector of claim 17, wherein said viral vector is an adeno-associated viral vector.

19. (Original) The vector of claim 16, wherein said promoter element directs expression of said polynucleotide in a retinal cell.

20. (Original) The vector of claim 16, wherein said promoter element directs expression of said polynucleotide in a photoreceptor cell.

21. (Original) The vector of claim 16, wherein said promoter element directs expression of said polynucleotide in a rod or a cone cell.

22. (Original) The vector of claim 16, wherein said promoter element directs expression of said polynucleotide in a Mueller cell, or a retinal pigement epithelium cell.

23. (Original) The vector of claim 16, wherein said promoter element comprises a mammalian rod opsin promoter element.

24. (Original) The vector of claim 16, wherein said promoter element comprises a constitutive or an inducible promoter element.

25. (Original) A virus comprising the ribozyme of claim 1, or a polynucleotide that encodes the ribozyme of claim 1.

26. (Original) The virus of claim 25, wherein said virus is an adenovirus or an adeno-associated virus

27. (Original) An adeno-associated viral vector comprising the ribozyme of claim 1, or a polynucleotide that encodes the ribozyme of claim 1.

28. (Original) The adeno-associated viral vector of claim 27, wherein said polynucleotide is operably linked to at least a first regulatory element that directs expression of said polynucleotide in a mammalian cell.

29. (Original) The adeno-associated viral vector of claim 28, wherein said regulatory element comprises a promoter that expresses said polynucleotide in a cell of a human eye.

30. (Original) A host cell that comprises:

(a) the ribozyme of claim 1;

(b) the vector of claim 16;

(c) the virus of claim 25; or

(d) the adeno-associated viral vector of claim 27.

31. (Original) The host cell of claim 30, wherein said cell is a mammalian host cell.

32. (Original) The host cell of claim 31, wherein said mammalian host cell is a human cell.

33. (Original) The host cell of claim 32, wherein said human cell is a retinal cell.

34. (Original) The host cell of claim 33, wherein said retinal cell is a photoreceptor cell.

35. (Original) The host cell of claim 34, wherein said retinal cell is a photoreceptor rod or cone cell.

36. (Original) A composition comprising:

(a) the ribozyme of claim 1;

(b) the vector of claim 16;

(c) the virus of claim 25; or

(d) the adeno-associated viral vector of claim 27.

37. (Original) The composition of claim 36, further comprising a pharmaceutical excipient.

38. (Original) The composition of claim 37, wherein said pharmaceutical excipient is suitable for ocular or subretinal administration to a mammalian eye.

39. (Original) The composition of claim 36, further comprising a lipid, a liposome, a nanoparticle, or a microsphere.

40. (Original) A kit comprising:

(a) (i) the ribozyme of claim 1;

(ii) the vector of claim 16;

(iii) the virus of claim 25; or

(iv) the adeno-associated viral vector of claim 27; and

(b) instructions for using said kit.

41. (Original) A kit comprising the composition of claim 36, and instructions for using said kit.

42. (Original) The kit of claim 41, further comprising device for delivering said composition to the eye, retina, or subretinal space of a mammal.

43. (Withdrawn) A method for decreasing the amount of mRNA encoding a selected polypeptide in a retinal cell of a mammalian eye, comprising providing to said eye an amount of the composition of claim 36, and for a time effective to specifically cleave said mRNA in said cell, and thereby decrease the amount of mRNA in said cell.

44. (Withdrawn) he method of claim 43, wherein said ribozyme specifically cleaves an mRNA encoding a polypeptide that causes a pathological condition in, or contributes to a disease, disorder, or dysfunction in a cell or a tissue of a mammalian eye.

45. (Withdrawn) The method of claim 43, wherein said composition is provided to said eye by direct administration, ocular injection, retinal injection, or subretinal injection.

46. (Withdrawn) The method of claim 44, wherein said pathological condition is selected from the group consisting of retinal degeneration, retinitis, macular degeneration, or retinopathy.

47. (Withdrawn) The method of claim 46, wherein said retinitis is retinitis pigmentosa.

48. (Withdrawn) The method of claim 46, wherein said pathological condition is autosomal dominant retinitis pigmentosa or autosomal recessive retinitis pigmentosa.

49. (Withdrawn) The method of claim 46, wherein said pathological condition is macular degeneration.

50. (Withdrawn) The method of claim 49, wherein said pathological condition is age-related macular degeneration.

51. (Withdrawn) The method of claim 46, wherein said pathological condition is retinopathy.

52. (Withdrawn) The method of claim 51, wherein said pathological condition is diabetic retinopathy.

53. (Withdrawn) A method for decreasing the amount of a selected polypeptide in a cell or tissue of a mammalian eye, comprising providing to said eye an amount of the ribozyme of claim 1 and for a time effective to specifically decrease the amount of said selected polypeptide in said cell or said tissue.

54. (Withdrawn) A method for decreasing the amount of a selected polypeptide in the eye of a mammal suspected of having a pathological condition selected from the group consisting of retinal degeneration, retinitis, macular degeneration, and retinopathy, comprising directly administering to said eye: (a) the ribozyme of claim 1, (b) the

vector of claim 16, (c) the virus of claim 25, or (d) the adeno-associated viral vector of claim 27, in an amount and for a time effective to specifically cleave an mRNA encoding said selected polypeptide, and thereby decreasing the amount of said polypeptide in said eye.

55. (Withdrawn) A method for treating, decreasing the severity, or ameliorating the symptoms of a pathological condition that results from the expression of at least a first selected polypeptide in a cell or a tissue of a human eye, said method comprising directly administering to said eye: (a) the ribozyme of claim 1, (b) the vector of claim 16, (c) the virus of claim 25, or (d) the adeno-associated viral vector of claim 27, in an amount and for a time effective to treat, decrease the severity, or ameliorate the symptoms of said pathological condition.

56. (Withdrawn) The method of claim 55, wherein said symptoms are selected from the group consisting of atrophic lesions of the eye, pigmented lesions of the eye, blindness, a reduction in central vision, a reduction in peripheral vision, and a reduction in total vision.

57. (Withdrawn) A method for decreasing the progression of a degenerative pathological condition of a mammalian eye, comprising providing to said eye: (a) the ribozyme of claim 1, (b) the vector of claim 16, (c) the virus of claim 25, or (d) the adeno-associated viral vector of claim 27, in an amount and for a time effective to decrease the progression of said degenerative pathological condition.

58. (New) A ribozyme that specifically cleaves an mRNA encoding a polypeptide that causes or contributes to the disease, disorder, or dysfunction of a cell or a tissue of a mammalian eye, wherein said ribozyme comprises the sequence of SEQ ID NO:100.

59. (New) A ribozyme that specifically cleaves an mRNA comprising the sequence of SEQ ID NO:88.

## 2. RESPONSE/REMARKS

### 2.1 STATUS OF THE CLAIMS

Since Applicants' previous amendment of 11/9/05 was not entered into the record, Applicants have utilized the claims of record prior to the non-entered amendment as the basis for the present amendment.

Claims 1-57 were pending at the time of the Initial Office Action/Restriction Requirement.

Claims 43-57 have been withdrawn from consideration, with traverse, as being directed to the non-elected Group II invention.

Claims 6, 7, 10-13 have been withdrawn from consideration, with traverse, as being directed to the non-elected "further restriction" aspect of the Group I invention.

Claim 8 has been amended herein.

Claims 58 and 59 have been added herein.

All pending claims read on the elected Group I invention and further read on the "further restriction" aspect as imposed by the Examiner, which required Applicants to elect a single ribozyme sequence and a single ribozyme target sequence for initial prosecution on the merits.

Claims 1-5, 8-9, and 14-42 are generic to the "further restriction" aspect of the Group I invention, and Applicants understand initial examination of these claims will be limited to the extent that they read on the two elected sequences. Upon allowance of the elected sequences, however, Applicants expect that the generic claims will be reexamined to the full extent of the claimed subject matter.

Claims 58 and 59 specifically read on the one target sequence and the one ribozyme sequence imposed by the Examiner in the "further restriction" aspect of the Group I restriction requirement.

Claims 1-59 are now pending in the case.

Applicants certify no new matter is added by the introduction of the present amendment. Support for the newly-added claims can be found throughout the Specification and the original claims. Applicants authorize the Assistant Commissioner to deduct any fees necessary for any reason in conjunction with the present amendment from Deposit Account No. 08-1394.

## 2.2 ATTORNEY DOCKET NUMBER

Applicants appreciate the Office's correct notice of Applicants' undersigned representative's affiliation with Haynes and Boone, LLP (customer number 0027683), and correction of the Attorney Docket number for this case to 36689.140. Applicants appreciate the Examiner's correction of the records to permit proper handling of all subsequent communication with the undersigned representative.

## 2.3 APPLICANTS TRAVERSE THE INITIAL RESTRICTION REQUIREMENT

The Original Office Action of 09/09/05 at page 2 noted that the Office considered two distinct inventions were presently claimed in the application, and therefore imposed a restriction.

The two inventions, defining compositions of matter and methods for their use are defined as:

> Group I. Claims 1-42 drawn to a ribozyme that specifically cleaves an mRNA encoding a polypeptide to a disease of the eye (Class 536, Subclass 24.5).
>
> Group II. Claims 43-57 drawn to a method for decreasing the amount of mRNA encoding a selected polypeptide in the eye and to a method of treating a condition that results from expression of a selected polypeptide of the eye, comprising administering a ribozyme that cleaves the selected mRNA (Class 435, Subclass 6 and 375).

In their original response to the First Action, dated 11/09/05, Applicants did not contest this Restriction, and elected to prosecute without traverse, the subject matter of the Group I invention.

In view of the present Notice of Non-Responsive Amendment, however, Applicants now, in order to permit later reconsideration and/or petition of this restriction as required by 37 CFR 1.143 and 1.144, make the election to prosecute the subject matter of the Group I invention *with traverse*.

Applicants specifically incorporates herein by reference in its entirety all of the remarks and arguments previously made in the response submitted to the Office on 11/9/05.

However, since the Current Action indicates that the previous amendment was not entered, Applicants make the present Amendment based upon the original claims in the application. Applicants specifically confirm the non-entry of the previous amendment of 11/9/05 as indicated by the present Action, and therefore, has submitted herewith a new listing of claims based upon the claims pending *prior to* the response filed on 11/9/05.

## 2.4 APPLICANTS TRAVERSE THE "FURTHER RESTRICTION" REQUIREMENT OF GROUP I

### 2.4.1 THE "FURTHER RESTRICTION" OF GROUP I IS IMPROPER

The Original Office Action at page 3, 1st paragraph, indicates that "should applicants elect to prosecute Group I, this group is subject to an additional restriction since claims 2, 3, 4, 5, 7, 8, 9, 10, 12, and 13 are" not considered to be a proper genus/Markush."

Applicants again respectfully traverse and renew their objection to this "further restriction." First, contrary to the Office's position, the cited claims ARE in proper Markush language. For example, original claim 2 is directed to a ribozyme "wherein said ribozyme specifically cleaves an mRNA encoding an IGF-1 receptor polypeptide selected from the group

consisting of rod opsin, RP1, RDS/Peripherin, iNOS, $A_{2B}$ receptor, IGF-1 receptor, alpha 1, alpha 3, and alpha V. This language is clearly proper, and thus the Office cannot impose "further restriction" because of incorrect Markush language.

Next, the Action at page 3, 2nd paragraph, states that "claims 2, 3, 5, 7-12 and 13 specifically claims (*sic*) mRNA encoding a polypeptide as listed or mRNA that comprises a nucleotide sequence as listed."

Again, Applicants respectfully traverse. Contrary to what the Examiner asserts, claims 2, 3, 5, 7-12, and 13 do **NOT** claim "mRNA encoding a polypeptide..." These claims are directed to a subgenus of ribozymes as claimed in claim 1. It is for this precise reason that the claim *depends* from claim 1, and is a proper subgenus of ribozymes claimed in linking claim 1.

The delineation of this genus/subgenus in original claims 1 and 2-4 is quite clear. For the Office to insist that these are improper, would be as absurd as considering that a generic claim directed to "a chair coated with a primary color paint" is not properly limited by a subsequent dependent claim that recites "wherein the primary color paint is selected from the group consisting of red and blue". The second claim isn't directed to red or blue *paint*... it is directed to a sub-population of painted chairs.

### 2.4.2 The Claimed Species are Proper Elements of the Genus

The Original Action stated, "Although the specific mRNA as listed and the mRNA sequences claimed each can be targeted and cleaved by the claimed ribozyme, the instant mRNA and mRNA sequences are considered to be unrelated, since each is structurally and functionally independent and distinct for the following reasons: each mRNA has a unique nucleotide sequence, each mRNA can be targeted by a different ribozyme, and each mRNA do not share a

common structure. As such the Markush/genus of the mRNA in 2, 3, 5, 8-11, and 13 are not considered to constitute a proper genus, and are therefore subject to restriction (*sic*)."

These claims all depend from claim 1, which is directed to "A ribozyme that specifically *cleaves* an mRNA that encodes a polypeptide. These claims are proper dependencies of Claim 1.

### 2.4.3 THE HOLDING THAT A SEARCH OF MORE THAN ONE DNA SEQUENCE REPRESENTS AN UNDUE BURDEN ON THE OFFICE IS BOTH ARBITRARY AND CAPRICIOUS

The Original Restriction in the Office Action dated 09/09/2005 at page 4 states "Furthermore, a search of more than one (1) of the ribozyme sequences claimed in claims 3 and 4 presents an undue burden on the Patent and Trademark Office due to the complex nature of the search and corresponding examination of more than one (1) of the claimed ribozyme sequences."

Applicants again respectfully traverse, and note for the record that searching of oligonucleotide sequences against databases of known sequences has been available and routine to the skilled artisan in the molecular biology field for nearly two decades. Moreover, these searches are automated and performed with the aid of computers using well-known and previously-available algorithms and sophisticated search engines. The searching of multiple sequences is not analogous to searching through shoes and shoes of published patents to find sequences that match. The searching process allows one to submit any number of sequences for electronic search, and that search is able to scan millions of documents and sequences in a manner of minutes to identify references that teach homologous, related, or identical sequences.

37 C. F. R. §1.141 provides that "a reasonable number of species" can be searched without undue burden upon the Office, and this standard has been in effect for almost a decade in the Office. Concerning nucleotide sequences specifically, MPEP 803.04 states in relevant part:

> "It has been determined that normally ten sequences constitute a reasonable number for examination purposes. Accordingly, in most cases, up to ten

> independent and distinct nucleotide sequences will be examined in a single application without restriction. In addition to the specifically selected sequences, those sequences which are patentably indistinct from the selected sequences will also be examined. Furthermore, nucleotide sequences encoding the same protein are not considered to be independent and distinct inventions and will continue to be examined together."

One need only examine the thousands of US patents that have issued in the last 10 years that claim more than 1 sequence to discover that the sequence process is neither "undue" or "burdensome".

Moreover, MPEP §2434 *specifically* addresses the issue of what constitutes a "reasonable number" of sequences for an examination in the Office.

In pertinent part, the guideline states:

> The U.S. Patent and Trademark Office published its policy for the examination of patent applications that claim large numbers of nucleotide sequences in the *Official Gazette*, 1192 O.G. 68 (November 19, 1996). Nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U. S. C. § 121. Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U. S. C. § 121 and 37 C. F. R. § 1.141. **In establishing the new policy, the Commissioner has partially waived the requirements of 37 C. F. R. §1.141 and will permit a reasonable number of such nucleotide sequences to be claimed in a single application. Under this policy, in most cases, up to 10 independent and distinct nucleotide sequences will be examined in a single application without restriction.** Those sequences which are patentably indistinct from the sequences selected by the applicant will also be examined. Nucleotide sequences encoding the same protein are not considered to be independent and distinct and will continue to be examined together. In some exceptional cases, the complex nature of the claimed material may necessitate that the reasonable number of sequences to be selected be less than 10." (emphasis added)

Applicants again renew their objection to this characterization of the species of the ribozymes that form one aspect of the present invention.

Applicants again assert that if it were the intent of the Congress to only permit an Applicant to obtain a patent on a *single species* of a *single genus*, then there would be absolutely no need for the Statutes and the Code to permit and to provide for Markush language, generic claims, linking claims, rejoinder, election of species, and so on. In fact, the entire discussion of a "species election" would be moot, if a patentee were only allowed to present a claim to a single example of a single restriction "group."

The very fact that the Code specifically provides for the examination of generic and sub-generic inventions, and that the Office has historically had a stated a policy of searching about 10 sequences in a given application, is evidence that there is no "undue burden" on the Office to examine 10 sequences. Likewise, if this were not the intent of the Congress, why are there literally thousands of patents issued by the Office from the present art unit that contain claims directed to both the genus of a collection of species, and claims directed to the various species themselves.

Applicants remain utterly perplexed at the propriety of the present restriction requirement, and the fact that it seems clearly to contradict years of examination precedent by the Office, particularly within Technology Center 1600.

Applicants again urge the Office to be consistent in the application of its policies and guidelines and to permit the searching of more than one ribozyme or more than one ribozyme target sequence in the present application. To do otherwise would represent an arbitrary and capricious action that would unfairly injure the Applicants' attempt to obtain patent protection for particular aspects of their invention.

## 2.5 APPLICANTS' EARLIER REQUEST FOR RECONSIDERATION WAS IGNORED

In Applicants' initial response to the Restriction, they formally requested that the restriction be reconsidered, and that the "further restriction" aspect with respect to the Group I invention (for which there appears to be no Statutory basis) be vacated, and if *absolutely* necessary, that aspect of the Action be reconsidered as an election of species from within the genus of nucleotide sequences of the ribozyme compositions and/or their target sequences..

Applicants argued to prosecute the subject matter of the Group I invention, without traverse, and to proceed with an election of species, if necessary, to begin prosecution on the merits.

It is clear from the 4-paragraph Office Action subsequently by the Office that the Examiner did not seriously consider Applicants' amendment and/or their Response and argument for reconsideration of the Action. The "form paragraph" nature of the 2 page reply by the Office is clear evidence that the various arguments and reasoning set forth in Applicants' prior 20+ page response was largely ignored.

Applicants are disappointed by the Office's apparent unwillingness to proceed with examination in an interest of expediency and fairness to this small-entity Applicant.

## 2.6 APPLICANTS REQUEST RECONSIDERATION UNDER 37 C. F. R. § 1.143

Pursuant to 37 C. F. R. § 1.143, which states in pertinent part::

> If the applicant disagrees with the requirement for restriction, he may request reconsideration and withdrawal or modification of the requirement, giving the reasons therefor. In requesting reconsideration the applicant must indicate a provisional election of one invention for prosecution, which invention shall be the one elected in the event the requirement becomes final. The requirement for restriction will be reconsidered on such a request. If the requirement is repeated and made final, the examiner will at the same time act on the claims to the invention elected.

Applicants also refer to the following pertinent part of M. P. E. P. § 806.04:

"Where an application includes claims directed to different embodiments or species that could fall within the scope of a generic claim, restriction between the species may be proper if the species are independent or distinct. However, 37 C. F. R. §1.141 provides that an allowable generic claim may link a reasonable number of species embraced thereby.

The practice is set forth in 37 C. F. R. § 1.146," which reads as follows:

"In the first action on an application containing a generic claim to a generic invention (genus) and claims to more than one patentably distinct species embraced thereby, the examiner may require the applicant in the reply to that action to elect a species of his or her invention to which his or her claim will be restricted if no claim to the genus is found to be allowable. However, if such application contains claims directed to more than a reasonable number of species, the examiner may require restriction of the claims to not more than a reasonable number of species before taking further action in the application."

## 2.7 APPLICANTS GIVE CONSTRUCTIVE NOTICE OF THEIR RIGHT TO PETITION UNDER 37 C. F. R. § 1.144

Should a final requirement for restriction be entered in the present case despite Applicants' earlier arguments against the same, despite Applicants' request for vacation of further restriction and imposition of species election, and despite Applicants' formal request herein for Reconsideration, Applicants hereby give constructive notice of their right to Petition the final holding of restriction to the Group Director pursuant to 37 C. F. R. § 1.144. As provided by the Rule, Applicants currently defer petition until after final action or allowance of the claims provisionally elected.

## 2.8 APPLICANTS' PROVISIONAL ELECTIONS

In an effort to comply with both the spirit of the Examiner's earlier Action, and in order to facilitate initial search and examination of the application, Applicants previously offered a voluntary species/subspecies election to logically facilitate an expedient prosecution that balanced the rights of the Applicants with the Examination burden on the Office. Applicants attempted to comply with the spirit of the Restriction Requirement by reducing the number of "species" for examination to a "reasonable number" using the guidelines as set forth in M. P. E. P. §2434, and previously requested that a total of ten species be considered, each in succession, if allowable subject matter is identified upon consideration of the initial species election herein.

Applicants previously indicated their consent to elect the "IGF-1 Receptor-specific mRNA target" species of ribozymes for first prosecution on the merits upon vacation of the "further restriction" and issuance of a species election for the mRNA target sequences cleaved by the claimed ribozyme compositions.

Applicants' request, however, appears to have gone unconsidered by the Office since it was followed by the instant "Notice of Non-Responsive Amendment." To that end, Applicants rescind their earlier proposed claim amendments and proposed species election, and now provide the following elections each with traverse, to be fully responsive to the pending Non-Responsive Notice:

### 2.8.1 APPLICANTS PROVISIONALLY ELECT THE GROUP I INVENTION

Applicants elect to prosecute *with traverse* the subject matter of Claims 1-42, the Group I invention.

**2.8.2 APPLICANTS PROVISIONALLY ELECT A SINGLE RIBOZYME TARGET SEQUENCE**

Applicants further elect to prosecute *with traverse* the single ribozyme target, SEQ ID NO:88.

**2.8.3 APPLICANTS PROVISIONALLY ELECT A SINGLE RIBOZYME SEQUENCE**

Applicants further elect to prosecute *with traverse* the single ribozyme sequence, SEQ ID NO:100.

**2.9 APPLICANTS RENEW THEIR REQUEST FOR REJOINDER OF THE GROUP II INVENTION UPON ALLOWANCE OF THE GROUP I INVENTION**

Applicants again note for the record that under the current Statutes, and consistent with the C.F.R., the M.P.E.P, and TC1600 restriction training materials, if the compositions of the Group I restriction are elected for prosecution, then the subject matter of the Group II invention (directed to *methods of using the compositions of Group I*), is subject to rejoinder upon the allowance of the corresponding composition claims.

Applicants again state their affirmative intention to seek rejoinder of the "process for using" claims upon allowance of claims directed to the products claimed in the Group I invention.

Referring again to the pertinent part of M. P. E. P. § 821.04(b):

> "Where claims directed to a product and to a process of making and/or using the product are presented in the same application, applicant may be called upon under 35 U. S. C. § 121 to elect claims to either the product or a process....(T)he claims to the non-elected invention will be withdrawn from further consideration under 37 C. F. R. § 1.142.*(H)owever, if applicant elects a claim(s) directed to a product which is subsequently found allowable, withdrawn process claims which depend from or otherwise require all the limitations of an allowable product claim will be considered for rejoinder.* All claims directed to a non-elected process invention must depend from or otherwise require all the limitations of an allowable product claim for that process invention to be rejoined. Upon rejoinder of claims directed

to a previously non-elected process invention, the restriction requirement between the elected product and rejoined process(es) will be withdrawn." (emphasis added).

Thus, by constructive election of the products of the Group I invention for initial prosecution on the merits, Applicants again affirmatively state their intention of requesting proper rejoinder of claims directed to a process of using such compositions (i.e. the subject matter of the Group II invention) upon allowance of the subject matter of the Group I invention.

## 2.10 REQUEST FOR EXAMINER/PRACTICE SPECIALIST INTERVIEW

Applicants hereby request an interview with the Examiner and a TC1600 Practice Specialist *before the issuance of a first Office Action* on the merits to specifically address the unusual nature of the complex restriction imposed upon, and now reiterated to, Applicants. Pursuant to 37 C. F. R. § 1.133 and M. P. E. P. §713.01, such an interview is proper, and Applicants respectfully request that the Examiner contact the undersigned representative within 30 days' receipt and consideration of the present paper.

## 2.11 CONCLUSION

In conclusion, in light of the foregoing remarks, Applicants believe that the concerns set forth in the Notice of Non-Responsive Amendment and the original Restriction Requirement have now been fully addressed. Favorable consideration of the pending claims is therefore respectfully requested. Should the Examiner have any questions, a telephone call to the undersigned Applicants' representative would be appreciated.

Respectfully submitted,

Mark D. Moore, Ph.D.
Registration No. 42,903

Date: May 23, 2006
HAYNES AND BOONE, LLP
901 Main Street, Suite 3100
Dallas, Texas 75202-3789
Telephone: 713-547-2040
Facsimile: 214-200-0853
H-612238_1.DOC